

# Exhibit A

# immuno biology 5

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

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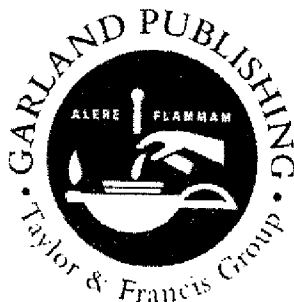
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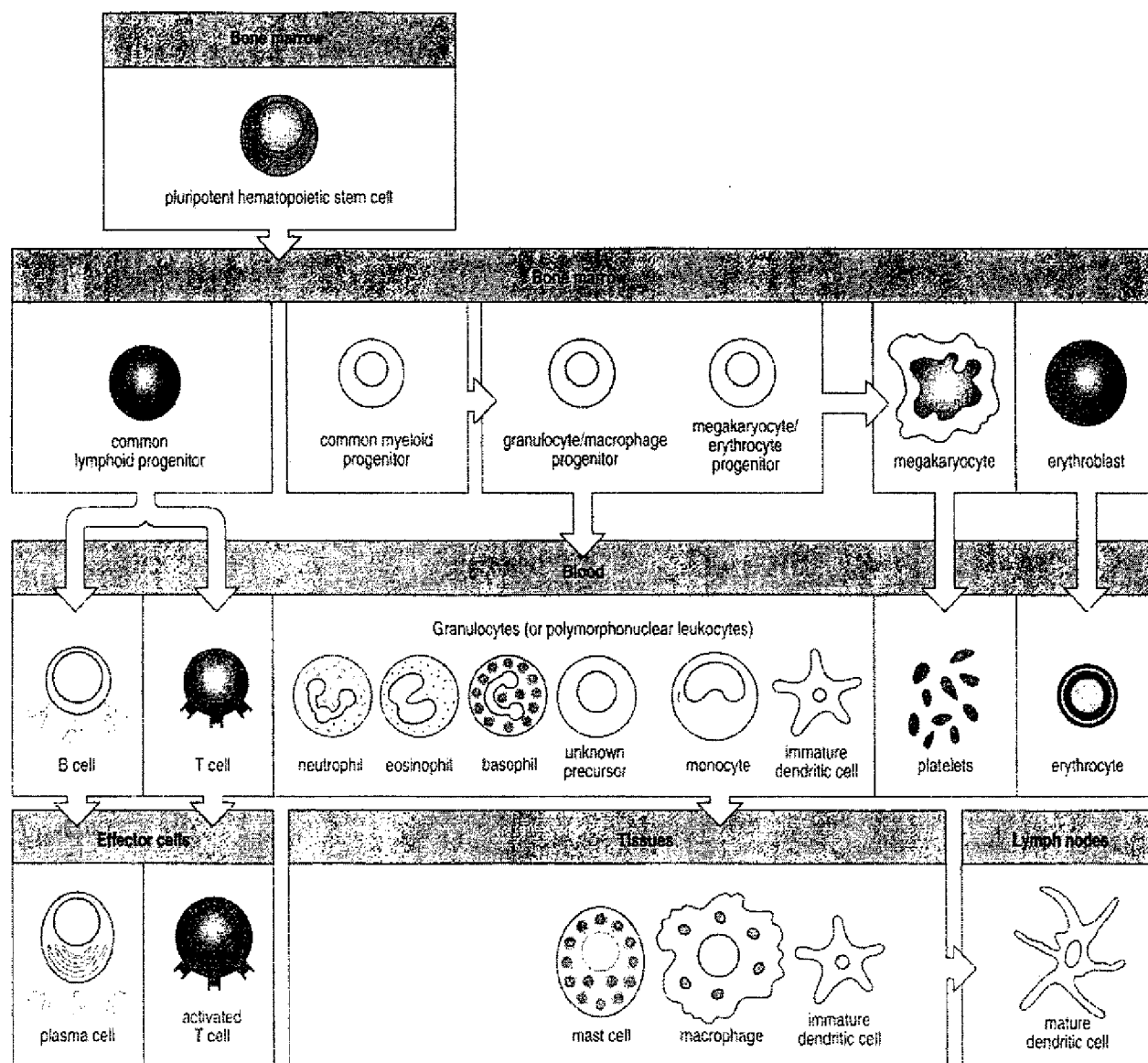
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**Fig. 1.3** All the cellular elements of blood, including the lymphocytes of the adaptive immune system, arise from hematopoietic stem cells in the bone marrow. These pluripotent cells divide to produce two more specialized types of stem cells, a common lymphoid progenitor that gives rise to the T and B lymphocytes responsible for adaptive immunity, and a common myeloid progenitor that gives rise to different types of leukocytes (white blood cells), erythrocytes (red blood cells that carry oxygen), and the megakaryocytes that produce platelets that are important in blood clotting. The existence of a common lymphoid progenitor for T and B lymphocytes is strongly supported by current data. T and B lymphocytes are distinguished by their sites of differentiation—T cells in the thymus and B cells in the bone marrow—and by their antigen receptors. Mature T and B lymphocytes circulate between the blood and peripheral lymphoid tissues. After encounter with antigen, B cells differentiate into antibody-secreting plasma cells, whereas T cells differentiate into effector T cells with a variety of functions. A third lineage of lymphoid-like cells, the natural killer cells, derive from the same progenitor cell but lack the antigen-specificity that is the hallmark of the adaptive

immune response (not shown). The leukocytes that derive from the myeloid stem cell are the monocytes, the dendritic cells, and the basophils, eosinophils, and neutrophils. The latter three are collectively termed either granulocytes, because of the cytoplasmic granules whose characteristic staining gives them a distinctive appearance in blood smears, or polymorphonuclear leukocytes, because of their irregularly shaped nuclei. They circulate in the blood and enter the tissues only when recruited to sites of infection or inflammation where neutrophils are recruited to phagocytose bacteria. Eosinophils and basophils are recruited to sites of allergic inflammation, and appear to be involved in defending against parasites. Immature dendritic cells travel via the blood to enter peripheral tissues, where they ingest antigens. When they encounter a pathogen, they mature and migrate to lymphoid tissues, where they activate antigen-specific T lymphocytes. Monocytes enter tissues, where they differentiate into macrophages; these are the main tissue-resident phagocytic cells of the innate immune system. Mast cells arise from precursors in bone marrow but complete their maturation in tissues; they are important in allergic responses.